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SPECIAL ARTICLE

ESMO Clinical Practice Guideline interim update on the treatment of locally advanced oesophageal and oesophagogastric junction adenocarcinoma and metastatic squamous-cell carcinoma

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INTRODUCTION

This interim update provides new recommendations for the following ESMO Clinical Practice Guideline (CPG): Oesophageal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up.[1]

View the original CPG here: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/clinical-practice-guideline-oesophageal-cancer.

MANAGEMENT OF LOCAL AND LOCOREGIONAL DISEASE

Locally advanced resectable disease (cT2-T4 or cN1-3 M0)

Adenocarcinoma. Treatment options for locally advanced resectable disease include perioperative chemotherapy (ChT) and neoadjuvant chemoradiotherapy (CRT). The first direct comparison of ChT versus CRT was provided by the phase III Neo-AEGIS trial, which compared preoperative CRT (CROSS study regimen) versus perioperative ChT [epirubicin—cisplatin—5-fluorouracil (ECF) or 5-fluorouracil—leucovorin—oxaliplatin—docetaxel (FLOT)] in patients with locally advanced resectable adenocarcinoma (AC) of the oesophagus or oesophagogastric junction (OGJ).[2] CRT was associated with higher rates of tumour regression and pathological complete response (CR) versus ChT but perioperative ChT was found to be non-inferior to CRT in terms of overall survival (OS) and disease-free survival. Notably, most patients (85%) in the ChT arm received the older and less effective ECF regimen rather than FLOT.

Data from the phase III ESOPEC trial comparing perioperative FLOT with preoperative CRT (CROSS regimen) in AC of the oesophagus were recently published.[3] At a median follow-up of 55 months, median OS (primary endpoint) was 66 months in the FLOT arm versus 37 months with CRT [hazard ratio (HR) 0.70, 95% confidence interval (CI) 0.53-0.92, $P = 0.01$]. Three- and 5-year OS rates with FLOT were 57.4% and 50.6%, respectively, and 50.7% and 38.7% with CRT, respectively. Progression-free survival (PFS) was also improved with FLOT compared with CRT (HR 0.66, 95% CI 0.51-0.85). The 90-day post-operative mortality rate was 3.1% in the FLOT arm and 5.6% in the CRT arm. These data suggest that perioperative FLOT is the preferred treatment option for locally advanced AC of the oesophagus and OGJ.

The ESOPEC findings are supported by the phase III TOPGEAR study, which reported that adding preoperative CRT to perioperative ChT improved pathological outcomes, but not OS, in 574 patients with resectable OGJ or gastric AC.[4] CRT was associated with a higher pathological CR rate (17% versus 8% with perioperative ChT; $P < 0.0001$), a higher major pathological response rate (<10% residual tumour present in 50% versus 29% with perioperative ChT) and greater tumour downstaging after resection. After a median follow-up of 67 months, however, there was no significant difference in OS or PFS between the study arms. Median OS was 46 months with CRT versus 49 months with ChT and median PFS was 31 months with CRT versus 32 months with ChT.

An updated algorithm for the management of local and locoregional resectable oesophageal and OGJ cancer is shown in Figure 1. New and/or updated recommendations are provided below.

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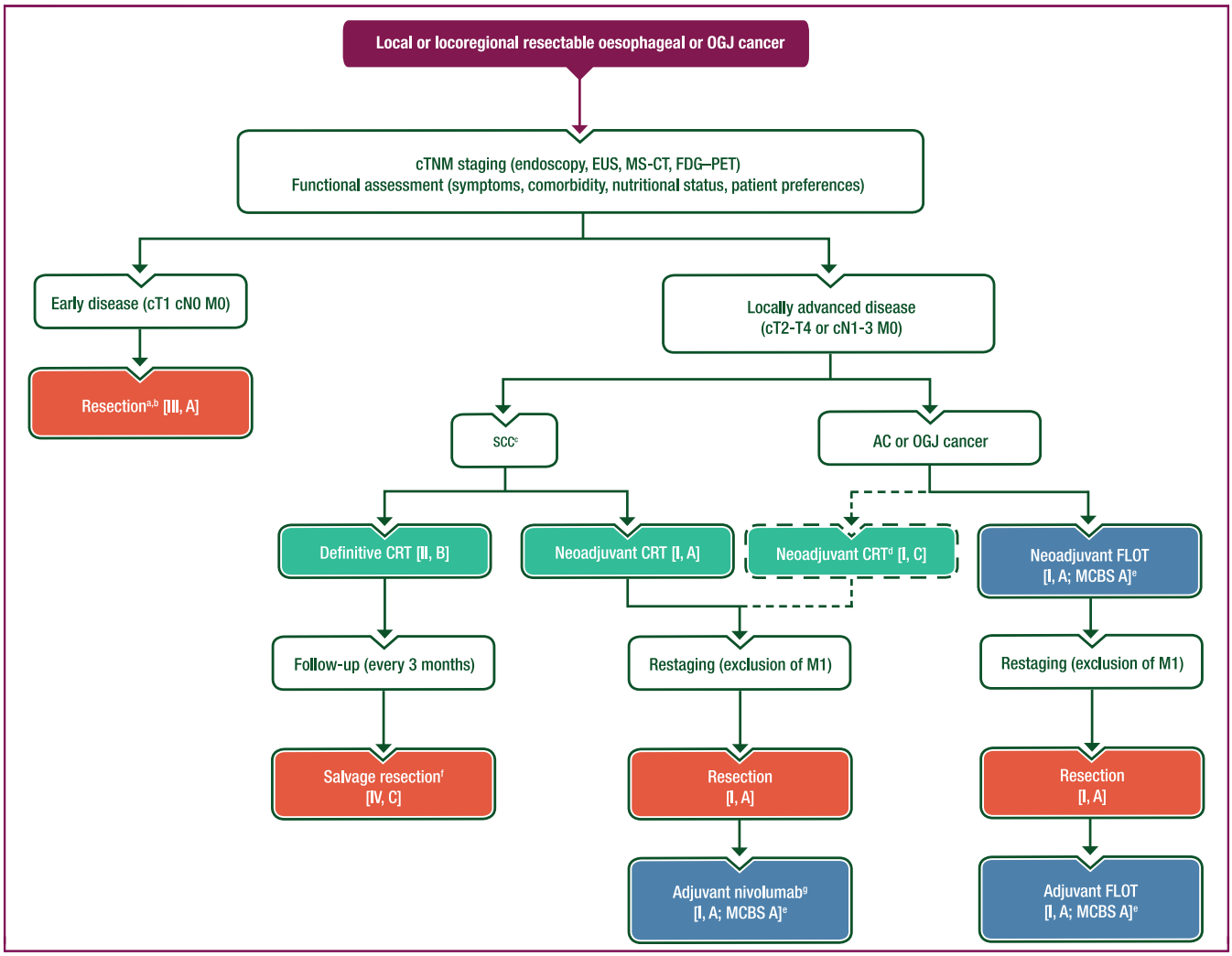

Figure 1. Management of local and locoregional resectable oesophageal and OGJ cancer.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: non-systemic anticancer therapies or combination of treatment modalities; white: other aspects of management and non-treatment aspects; dashed lines: optional therapy.
AC, adenocarcinoma; CPG, Clinical Practice Guideline; CRT, chemoradiotherapy; cTNM, clinical tumour—node—metastasis; EMA, European Medicines Agency; EUS, endoscopic ultrasound; FDA, Food and Drug Administration; FDG—PET, [^{18}F]2-fluoro-2-deoxy-D-glucose—positron emission tomography; FLOT, 5-fluorouracil—leucovorin—oxaliplatin—docetaxel; MCBS, Magnitude of Clinical Benefit Scale; MS-CT, multislice-computed tomography; OGJ, oesophagogastric junction; OS, overall survival; RT, radiotherapy; SCC, squamous-cell carcinoma.
[a]Criteria for endoscopic instead of surgical resection are specified in the CPG.[1]
[b]For patients unable or unwilling to undergo surgery, combined CRT is superior to RT alone.
[c]Evidence suggests that neoadjuvant CRT followed by surgery and definitive CRT is equally effective with regard to OS. Oesophageal surgery should be carried out in experienced (high-volume) centres only. For patients not willing to undergo oesophageal surgery or who are medically unfit for major surgery, definitive CRT should be preferred. Even many experienced centres prefer definitive CRT for oesophageal tumours with a very proximal/cervical location.
[d]May be considered if the patient is not suitable for FLOT.
[e]ESMO-MCBS v1.1[10] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[f]This is optional in the case of incomplete response to CRT or local relapse and should only be carried out in selected patients and experienced centres.
[g]With residual vital tumour in the resection specimen.

Recommendations

- Multimodality treatment should be considered in all patients with locally advanced resectable oesophageal cancer [I, A].
- Patients with resectable, locally advanced AC of the oesophagus or OGJ should be treated with perioperative FLOT followed by surgery [I, A; ESMO-Magnitude of Clinical Benefit Scale (MCBS) v1.1 score: A].
- Neoadjuvant CRT may be considered if the patient is not suitable for FLOT [I, C].

MANAGEMENT OF ADVANCED AND METASTATIC DISEASE

First-line ChT plus immune checkpoint inhibitors or immune checkpoint inhibitors without ChT for oesophageal squamous-cell carcinoma

The first-line management of metastatic oesophageal squamous-cell carcinoma (SCC) has not changed, but new trials of immune checkpoint inhibitors have confirmed their efficacy in combination with ChT.

The phase III RATIONALE-306 study randomised patients with untreated, unresectable, locally advanced or metastatic oesophageal SCC to tislelizumab—ChT ($n = 326$) or placebo—ChT ($n = 323$).[5] ChT was an investigator-chosen platinum-based doublet. After a median follow-up of 16.3 months in the tislelizumab—ChT arm and 9.8 months in the placebo arm, median OS (primary endpoint) was 17.2 months with tislelizumab—ChT versus 10.6 months with placebo—ChT (stratified HR 0.66, 95% CI 0.54-0.80), regardless of programmed death-ligand 1 (PD-L1) status. The European Medicines Agency (EMA) has approved tislelizumab—ChT for patients whose tumours have a PD-L1 tumour area positivity (TAP) score ≥5%.

The phase III JUPITER-06 study evaluated toripalimab—cisplatin—paclitaxel versus placebo—cisplatin—paclitaxel followed by toripalimab or placebo maintenance in Chinese patients with untreated advanced oesophageal SCC.[6] Toripalimab was associated with significant improvements in PFS (HR 0.58, 95% CI 0.46-0.74, $P < 0.0001$) and OS (HR 0.58, 95% CI 0.43-0.78, $P = 0.0004$) compared with placebo. A recommendation cannot currently be provided for toripalimab as it has not been evaluated outside of a Chinese population.

Second and subsequent lines of treatment for oesophageal SCC

For patients with oesophageal SCC, second-line nivolumab or tislelizumab monotherapy are options based on the results of the phase III ATTRACTION-3[7] and RATIONALE-302[8] studies. Key data from ATTRACTION-3 are described in the original CPG.[1] In RATIONALE-302, 512 patients predominantly from Asia who had progressed after platinum-based ChT were randomised to receive tislelizumab or ChT (irinotecan, paclitaxel or docetaxel).[8] In the final analysis, median OS (primary endpoint) was significantly longer with tislelizumab versus ChT in the overall study population (8.6 months versus 6.3 months; HR 0.70, 95% CI 0.57-0.85, $P = 0.0001$) and in patients with a PD-L1 TAP score ≥10% (10.3 months versus 6.8 months; HR 0.54, 95% CI 0.36-0.79, $P = 0.0006$). Tislelizumab was associated with a higher objective response rate (ORR; 20.3% versus 9.8% with ChT) and a more durable antitumour response [median duration of response (DoR) 7.1 months versus 4.0 months with ChT]. A recent subgroup analysis of RATIONALE-302 evaluated the efficacy of tislelizumab in 108 patients from Europe and North America,[9] reporting an OS benefit consistent with the primary analysis (median OS 11.2 months with tislelizumab versus 6.3 months with ChT; HR 0.55, 95% CI 0.35-0.87). The HR was similar irrespective of PD-L1 TAP score (≥10% HR 0.47, 95% CI 0.18-1.21; <10% HR 0.55, 95% CI 0.30-1.01). Median PFS was 2.3 months with tislelizumab versus 2.7 months with ChT (HR 0.97, 95% CI 0.64-1.47). ORR was greater with tislelizumab (20.0%) versus ChT (11.3%) and responses were more durable (median DoR 5.1 months with tislelizumab versus 2.1 months with ChT).

An updated algorithm for the management of advanced oesophageal SCC is shown in Figure 2. New and/or updated recommendations are provided below.

Recommendations

First-line treatment for advanced oesophageal SCC

- Tislelizumab—ChT is recommended for the first-line treatment of advanced oesophageal SCC in patients with a PD-L1 TAP score ≥5% [I, A; ESMO-MCBS v1.1 score: 4; EMA approved, not Food and Drug Administration (FDA) approved].

Second and subsequent lines of treatment for advanced oesophageal SCC

- Tislelizumab [I, A; ESMO-MCBS v1.1 score: 4] or nivolumab [I, A; ESMO-MCBS v1.1 score: 3] are recommended for oesophageal SCC previously treated with platinum—fluoropyrimidine ChT.

METHODOLOGY

This eUpdate was developed in accordance with the ESMO standard operating procedures for eUpdate development (http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated in algorithms by ordering these options according to: level of evidence (LoE) and grade of recommendation (GoR); where equal, by ESMO-MCBS score; where equal, by alphabetical order. The relevant literature has been selected by the expert authors. A table of ESMO-MCBS scores is included in Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2025.104134. ESMO-MCBS v1.1[10] was used to calculate scores for new therapies/indications approved by the EMA or FDA (https://www.esmo.org/Guidelines/ESMO-MCBS). The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors. The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this eUpdate. LoEs and GoRs have been applied using the system shown in Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2025.104134.[11] Statements without grading were considered justified standard clinical practice by the authors. For future updates to the oesophageal cancer CPG, including eUpdates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/clinical-practice-guideline-oesophageal-cancer.

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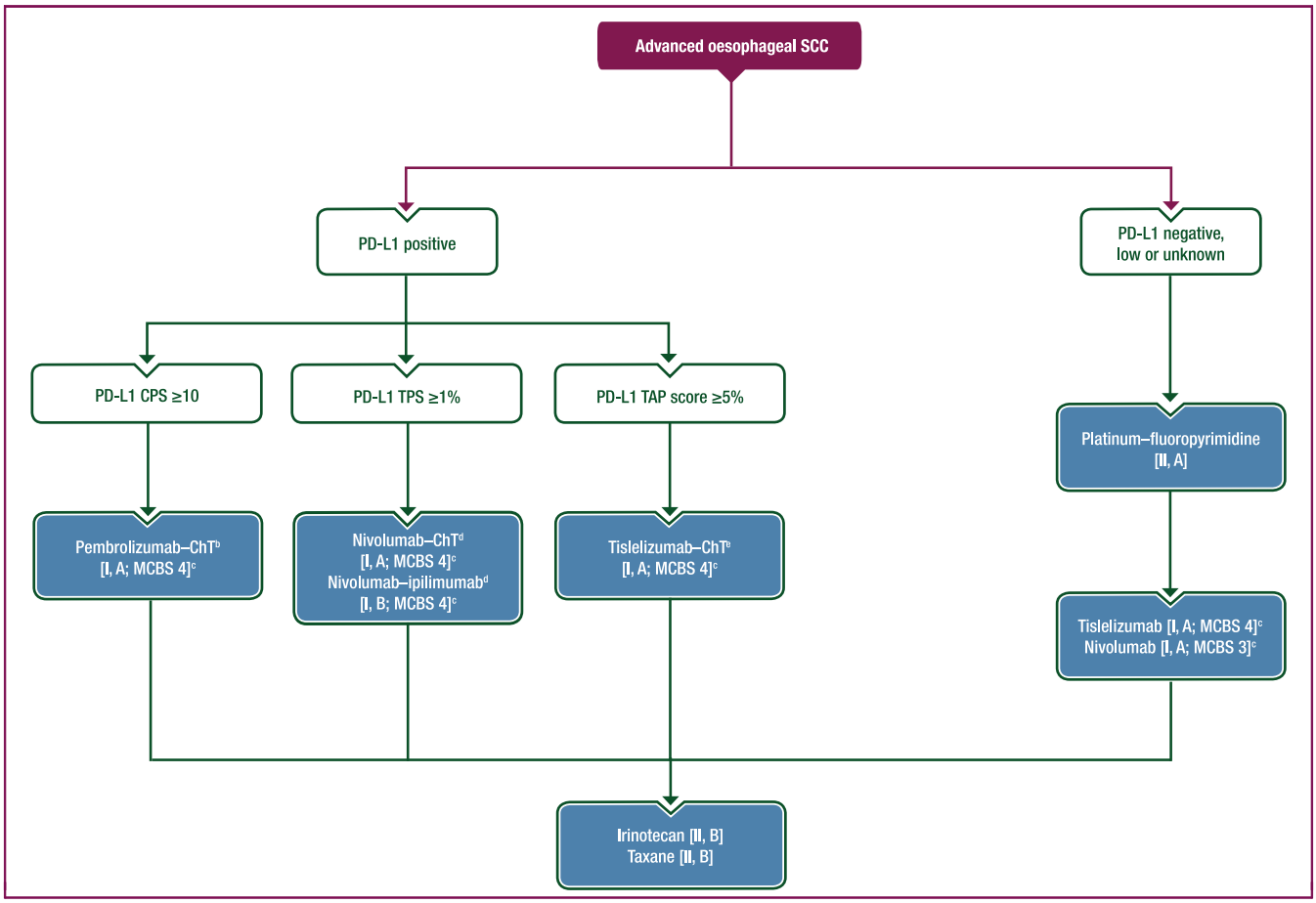

Figure 2. Management of advanced oesophageal SCC.[a]
Purple: algorithm title; blue: systemic anticancer therapy or their combination; white: other aspects of management and non-treatment aspects.
AC, adenocarcinoma; ChT, chemotherapy; CPG, Clinical Practice Guideline; CPS, combined positive score; EMA, European Medicines Agency; FDA, Food and Drug Administration; MCBS, Magnitude of Clinical Benefit Scale; OGJ, oesophagogastric junction; PD-L1, programmed death-ligand 1; SCC, squamous-cell carcinoma; TAP, tumour area positivity; TPS, tumour proportion score.
[a]For treatment of advanced oesophageal AC and OGJ cancer, see the ESMO CPG for gastric cancer.[12]
[b]EMA approval is for tumours with PD-L1 CPS ≥10, FDA approval is irrespective of PD-L1 expression.
[c]ESMO-MCBS v1.1[10] was used to calculate scores for therapies/indications approved by the EMA or FDA. The scores have been calculated and validated by the ESMO-MCBS Working Group and reviewed by the authors (https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-evaluation-forms).
[d]EMA approval is for tumours with tumour cell PD-L1 expression ≥1%, FDA approval is irrespective of PD-L1 expression.
[e]EMA approved, not FDA approved.

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